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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/015,399	01/29/98	HINKKANEN	A 2328-111

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EXAMINER	
LUBET, M	
ART UNIT	**PAPER NUMBER**
1644	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/015,399	Applicant(s) Hinkkanen ~~Hinkkanen~~
	Examiner Lubet	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Jun 11, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17* is/are pending in the application.

Of the above, claim(s) *11-16* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10 and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1 Claims 1-17 are pending. Examiner acknowledges election of Group I claims 1-10 and 17 and a species election of the fusion protein of Claim 3 in Paper 6 filed June 11, 1999. Claims 11-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-10 and 17 are under examination and are examined as they read upon a fusion protein comprising eptiope 771-979 of IA2, amino acid residues 102-585 of GAD, and 1-110 or PPINS.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant is requested to amend claim 3 to recite the SEQ ID NO:. For instance ". . .the epitope of GAD65 comprise amino acids 771-779 of SEQ ID NO:6. . ."

3. Applicant is reminded of the proper content of an Abstract of the Disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. The abstract of the disclosure is objected to because the abstract is two paragraphs. The abstract should be one paragraph (see MPEP 608.01 (b).

4. Claims 1-10 and 17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Reasons are set forth below.

A. Claim 1 is a Markush group but is improper form. The Markush groups recited in claim 1 should be amended to recite " A fusion protein having epitopes of at least two autoantigens selected from the group consisting of glutamic acid decarboxylases (GAD65), islet cell antigen (IA2) and preproinsulin (PINS) wherein said . . . "

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-5, 7-10 and 17 are rejected under 35 U.S.C. 103(a) as obvious over Rogers et al. US 5, 547,669 (issued August 20, 1996 filed Dec. 13, 1991) in view of Hummel et al. (J. Autoimmunity 9:427, 1996), Verge et al. (J. Autoimmunity 9:379, 1996), Rabin et al. US 5,200,318 (issued April 6, 1993, fled May 13, 1992), Borg et al. (Clinical Chemistry 43:2358, 1997), Berg et al. (J. Immunological Methods 164:221, 1993) and Wiest-Ladenburger et al. (Diabetes 46:565, 1997).

Claims 1-4 are drawn to fusion comprising epitopes of IA2, GAD65 and PPINS (preproinsulin). The elected species encompass a fusion protein comprising full length IA2, GAD65 and PPINS since the claims recite the term "comprises". Claims 5 and 6 are drawn to said fusion protein with a linker peptide provided with an affinity binding pair such as biotin-streptavidin. Claims 7-10 and 17 are drawn to DNA encoding the fusion protein and vectors comprising the DNA.

Rogers et al. teaches fusion proteins comprising epitopes of at least two proteins and the use of such proteins to assay for T cell reactivity or antibodies to the epitopes comprising the fusion proteins. Rogers et al. further teach that the epitopes may be derived from autoantigens (see abstract, column 6, lines 1-31, column 10, lines 31-60, column 13, lines 3-30, in particular). Rogers et al. also teach that the fusion protein can comprise epitopes of autoantigens of diabetes and that such autoantigens include insulin, GAD, PM-1 and carboxypeptidase (see column 12, lines 12, lines 24-30, in particular).

Rogers et al. also teach that the epitopes can be linked together by linkers comprising amino acid sequence. Rogers et al. disclose that the peptide linkers can comprise protease sensitive sites such as KK (Lys-Lys) or RR (Arg-Arg), thus disclosing fusion proteins comprising two or more epitopes linked by linker comprising lysine and arginine residues as is claimed in claim 4 of the instant specification (see column 15, lines 55-67, in particular).

Rogers et al. further teach that the fusion protein can be produced recombinantly or synthetically (see column 7, lines 61-67, in particular). Rogers et al. disclose that the fusion protein can be made recombinantly by making cDNA encoding the fusion protein, vectors comprising said cDNA and expressing the vector in E. coli host cell (see column 19, lines 1-30, in particular).

Rogers et al. also teach that the fusion protein which is provided with (comprises) a member of an affinity binding pair, histidine. (see column 19, lines 30-45, in particular). Rogers et al. teach that histidine residues allow purification of the fusion protein by binding the protein to solid phase comprising nickel (see column 19, lines 30-45, in particular). Thus a fusion protein comprising a histidine sequence is a fusion protein provided with a member of an affinity binding pair.

Rogers et al. does not exemplify a fusion product having an epitope of IA2, GAD and preproinsulin comprising the amino acid 771-979 of IA2, amino acid 102-585 of GAD and amino acids 1-110 of PPINS. The use of the term "comprising" in the claim language opens up the claims to read upon a fusion protein comprising the recited sequences but containing additional residues of the native protein or fusion proteins comprising intact IA2, GAD and PPINS.

The prior art teaches that patients with immune reactivity (serum antibody and/or T cell response) to IA2, GAD and preproinsulin are at risk for development of diabetes and that patients that have antibodies to more than one of these antigens are at increased risk for the development of diabetes.

Hummel et al. teach that of newly diagnosed diabetes patients all showed reactivity to at least one recombinant islet cells antigen selected from insulin, GAD 65, and IA2 and that humoral and cellular immune reactivity to multiple islet cell antigens are present in patients with newly diagnosed type 1 diabetes and in high risk relatives (see abstract, in particular). Hummel et al.

teach that antibodies and cell mediated immune responses to IA2 is a risk factor for the development of diabetes (see Figure 1 and 2 and page 428-429, in particular). Hummel et al. teach that assaying for the presence of immune response to more than one autoantigen may become of increasing value in the diagnosis or preclinical type diabetes.

Verge et al. teach that among first degree relatives of diabetes the five year risk of diabetes was 0% if antibodies to IAA, GAD, ICA512bcd are not detected, 15% if only one was positive, 44% if two were detected and 100% is all three were detected. Verge et al. teach that 76% of new onset patients are positive for two or more autoantibodies and 98% were positive for one or more and 0% of control tested positive for more than one autoantibody. Verge et al. also teach that with new onset insulin-dependent diabetes, the absence of any of these autoantibodies justifies the consideration of non-autoimmune forms of diabetes in the differential diagnosis (see abstract, Figure 1, Figure 3, and page 382, in particular).

Rabin et al. teach a method of diagnosing insulin dependent diabetes with an immunoassay which utilizes an immunoreagent comprising eptiopes of GAD and ICA512 and ICA 12 (see abstract and claims 1-21, in particular). Rabin et al. teach an immunoreagent that is a polymer backbone to which are attached multiples of one or more antigens and assays to determine reactivity of serum with immunoreagent (see column 7, lines 1-11 and column 7, line 24 through column 9, line 11, in particular). Rabin et al. also teach assays in which the specificity of the serum (IE reactivity to one of the antigen attached to the backbone) can be determined (see column 8, line 57 through column 9, line 9, in particular).

Borg et al. teach that assaying for antibodies to GAD and IA2 is useful in the diagnosis of diabetes and is an effective alternative to ICA assay. Borg et al. teach that the of ICA positive patient only 5% of patients lacked both IA2 antibody and anti-GAD antibody and 52% of the patients had both anti-IA2 and anti-GAD antibodies, 24% had only anti- IA2 antibody and 18% had only anti- GAD antibody (see page 2360, in particular). Borg et al. teach that by assaying for both IA2 and GAD antibody 95% of the ICA positive diabetes could be identified, but that 5%

ICA patients have antibodies to other antigens. Borg et al. also teach that in order to clarify the pathogenesis of IDDM determination of both antibodies to IA2 and GAD seem necessary.

Berg et al. teach that sera from patients with recent-onset diabetes, 14% of the patients sera contain insulin autoantibodies which strongly recognized recombinant preproinsulin. Berg et al. also teach that anti-GAD antibodies serves as the most relevant serological marker for ongoing β cell destruction and that generation of insulin autoantibodies alone confers relatively little risk for IDDM development (see abstract and page 22). Berg et al. teach cDNA encoding preproinsulin and vectors and E.coli cells comprising said cDNA. The recombinant preproinsulin peptide comprises a histidine hexapeptide and GST (see page 229, in particular) and that the GST moiety introduces an enterokinase site and histidine hexapeptide permits single step purification by affinity chromatography using metal chelating Sepharose charged to NI ions. (see page 229, in particular). Berg et al. teach that the use of preproinsulin to assay for autoantibodies in patients permits the detection of antibodies directed against the C-peptide or signal peptide. Berg et al. further teach that 11.6% of ICA positive sera were positive for anti-preproinsulin antibodies but that none of ICA positive serum were positive for anti-insulin antibodies (see page 229 and 230, in particular).

Wiest-Ladenburger et al. teach that in most individuals developing IDDM, cytoplasmic islet cells antibodies (ICAs) circulate before and at the onset of the disease. Wiest-Ladenburger also tech ICA are the classical serological markers for diagnosis and prediction of IDDM, but high technical demands have limited the widespread use of histochemical ICA test. Wiest-Ladenburger also teaches that antibodies to IA2 and GAD65 represent major subfraction of ICA. Wiest-Ladenburger also teach that ICAs also react with carboxypeptidase H, ICA69, proinsulin or insulin. Wiest-Ladenburger further teach that amino acid 603-979 of IA2 comprise epitopes recognized by ICAs. Wiest-Ladenburger also teach that a one-step assay for autoantibodies to IDDM autoantigens reduces costs and effort by more than 40% compared with separate testing, allowing an efficient large-scale screening of sera (see abstract and page 565 in particular).

Thus the prior art teaches that patients with immune responses (antibodies and/or T cell reactivity) to GAD, IA2 and preproinsulin are at risk for the development of diabetes and that measuring antibodies to GAD, IA2 and preproinsulin are useful in the diagnosis of diabetes. The art teaches that that patients that have antibodies to more than one of these antigens are at increased risk for the development of diabetes and the advantages of testing for reactivity to more than one IDDM autoantibody.

Therefore one with ordinary skill in the art at the time of the invention would have been motivated to make a fusion protein such as the one taught by Rogers et al. in which the autoantigens in the fusion protein comprise IA2, GAD and preproinsulin with the expectation that patients could be screened for immune responses to the fusion protein to identify patients at risk for development of diabetes as is taught by Rabin et al. or Wiest-Ladenburger et al. since the prior art teaches that detection of immune responses to IA2, GAD and preproinsulin antibodies are useful in the diagnosis of diabetes and the identification of patients at risk for diabetes. One would have been motivated to use such a fusion protein comprising the autoantigens in place of the immunoreagents taught by Rabin et al. for ease of manufacture and consistency of the immunoreagent. One with ordinary skill in the art would have been motivated to combine the antigens into one immunoreagent (fusion protein) since the prior art teaches patients that have antibodies to more than one of these antigens are at increased risk for the development of diabetes and that one-step assays that simultaneously measure antibodies to more than one IDDM autoantigen allow for efficient and cost effective screening of sera. Fusion proteins comprising the linkers taught by Rogers et al. meet the claim limitation of claim 4. Fusion protein comprising histidine hexapeptide linked to the linkers taught by Rogers et al. meet the claim limitations of claim 5 since histidine is a member of an affinity binding pair and the art teaches that fusion proteins which comprise the histidine hexapeptide can be readily purified in a one-step purification protocol by binding the protein onto a Ni-Sepharose column. One with ordinary skill in the art would have been motivated to provide the fusion protein with a binding partner such as

histidine to aid in the purification of the fusion protein as taught by Rogers et al. and Berg et al. or for use in immunoassays taught by Rabin et al.

One with ordinary skill in the art would have been motivated to make the fusion protein recombinantly by making a cDNA encoding the fusion protein, a vector expressing the DNA and expressing the vector in E. coli using the methods taught in the prior art to make fusion proteins with the expectation that the fusion protein encoded by the cDNA could be used in assays to screen for immune responses to the autoantigens comprising the fusion protein.

7. Claims 1-10 and 17 under 35 U.S.C. 103(a) as obvious over Rogers et al. US 5, 547,669 (issued August 20, 1996, filed Dec. 13, 1991) in view of Hummel et al. (J. Autoimmunity 9:427, 1996), Verge et al. (J. Autoimmunity 9:379, 1996), Rabin et al. US 5,200,318 (issued April 6, 1993, fled May 13, 1992), Borg et al. (Clinical Chemistry 43:2358, 1997), Berg et al. (J. Immunological Methods 164:221, 1993) and Wiest-Ladenburger et al. (Diabetes 46:565, 1997) and further in view of WO 94/07464 (issued March 16, 1994).

Rogers et al. US 5, 547,669, Hummel et al. , Verge et al., Rabin et al. US 5,200,318, Borg et al., Berg et al. (J. Immunological Methods 164:221, 1993) and Wiest-Ladenburger et al. have been discussed. The invention claimed in claim 6 differs from the prior art in that the fusion protein comprises biotin or streptavidin.

However, WO 94/07464 teaches GAD labeled with biotin and the use of the biotin labeled GAD in immunoassays to detect antibodies to GAD. WO 94/07464 also teaches that autoantibodies to β-islet cell GAD my be extracted from patients serum, by binding to GAD and the complex to an insoluble or solid support. (See page 15, line 8 through page 16, line 20.

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time of the invention to make a fusion protein comprising IA2, GAD and preproinsulin for the

reasons discussed supra in which biotin is the binding member with the expectation that the biotin labeled fusion protein could be used to in immunoassays to screen sera.

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet

TC

THOMAS M. CUNNINGHAM
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